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Case report of successful low-dose, ultra-slow infusion thrombolysis of prosthetic mitral valve thrombosis in a high risk patient after redo-mitral valve replacement

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Abstract: Background An increase in transvalvular pressure gradient of prosthetic valve should always raise suspicion for obstructive valve thrombosis. A multimodality diagnostic approach including transthoracic echocardiography, transoesophageal echocardiography (TOE), cinefluoroscopy, or computed tomography (CT) is necessary for a prompt diagnosis. The management of mechanical prosthetic valve thrombosis (PVT) is high risk in any therapeutic option taken. Emergency valve replacement is recommended for critically ill patients. Fibrinolysis is an alternative for patients with contraindication to surgery or if surgery is not immediately available. Case summary A 52-year-old woman presented with symptoms and signs of cardiac congestion. On laboratory, brain natriuretic peptide was elevated and international normalized ratio (INR) was in subtherapeutic range. She underwent a mitral valve replacement with mechanical prosthesis 7 months before, because of a significant residual regurgitation after repair on the same year. TOE revealed severe stenosis of the prosthesis with immobile anterior disc but there was no mass present. CT revealed a minor lesion at the hinge points of the prosthesis without involvement of the ring, suggestive for thrombus. The initial fruitless management with intravenous (i.v) heparin in high therapeutic range was followed by a successful 'low-dose, ultra-slow' fibrinolysis. Discussion CT may help differentiate thrombus vs. pannus. The acute onset of symptoms, inadequate anticoagulation, and restricted leaflet motion increased the suspicion for PVT. The current European guidelines propose normal dose fibrinolysis. We performed 'low-dose, ultra-slow' fibrinolysis due to lower bleeding risk with successful results. Low dose should be considered as alternative to normal dose fibrinolysis or urgent surgery.

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Case report of successful low-dose, ultra-slow infusion thrombolysis of prosthetic mitral valve thrombosis in a high risk patient after redo-mitral valve replacement

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Background

An increase in transvalvular pressure gradient of prosthetic valve should always raise suspicion for obstructive valve thrombosis. A multimodality diagnostic approach including transthoracic echocardiography, transoesophageal echocardiography (TOE), cinefluoroscopy, or computed tomography (CT) is necessary for a prompt diagnosis. The management of mechanical prosthetic valve thrombosis (PVT) is high risk in any therapeutic option taken. Emergency valve replacement is recommended for critically ill patients. Fibrinolysis is an alternative for patients with contraindication to surgery or if surgery is not immediately available.

Case summary

A 52-year-old woman presented with symptoms and signs of cardiac congestion. On laboratory, brain natriuretic peptide was elevated and international normalized ratio (INR) was in subtherapeutic range. She underwent a mitral valve replacement with mechanical prosthesis 7 months before, because of a significant residual regurgitation after repair on the same year. TOE revealed severe stenosis of the prosthesis with immobile anterior disc but there was no mass present. CT revealed a minor lesion at the hinge points of the prosthesis without involvement of the ring, suggestive for thrombus. The initial fruitless management with intravenous (i.v.) heparin in high therapeutic range was followed by a successful 'low-dose, ultra-slow' fibrinolysis.

Discussion

CT may help differentiate thrombus vs. pannus. The acute onset of symptoms, inadequate anticoagulation, and restricted leaflet motion increased the suspicion for PVT. The current European guidelines propose normal dose fibrinolysis. We performed 'low-dose, ultra-slow' fibrinolysis due to lower bleeding risk with successful results. Low dose should be considered as alternative to normal dose fibrinolysis or urgent surgery.

Keywords

Case report • Echocardiography • Computed tomography • Valve disease • Mechanical prosthesis • Thrombolysis

Learning points

- CT should be performed to differentiate pannus vs. thrombus if no mass is detected during transoesophageal echocardiography.
- Low-dose, ultra-slow fibrinolysis should be considered as an alternative to normal dose fibrinolysis or urgent surgery.

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Introduction

Every replacement of a diseased heart valve with either biological or mechanical prosthesis exchanges the native disease for prosthesis-related complications. The most common complications include prosthetic valve obstruction, embolic events, bleeding, infective endocarditis, and haemolysis. An obstruction may be caused by thrombosis and/or pannus formation. A prosthetic valve thrombosis (PVT) can be symptomatic or subclinical (non-obstructive). Prosthetic valve obstruction is defined as an increase in the mean gradient on steady-state haemodynamic condition, estimated with transthoracic echocardiography (TTE), above the expected normal range for the specific type and size of the prosthesis. The reported incidence of symptomatic obstructive mechanical prosthesis ranges from 0.3% to 1.3% per year, with subtherapeutic anticoagulation been the major risk factor.^{1,2} Mitral mechanical PVT is reported to be twice as frequent as aortic mechanical PVT and rates of thromboembolism are higher for certain types of mechanical valves. PVT should be suspected in a patient with a new murmur, change in closing clicks, symptoms, and signs of heart failure or thromboembolic events. The initial evaluation is performed with TTE and additional imaging options include transoesophageal echocardiography (TOE), cardiac computed tomography (CT) or fluoroscopy. The choice between TOE and CT as additional imaging tools is made based upon availability, patient characteristics, prior test results, mechanical valve type/location, and local expertise.²

Timeline

November 2017	Diagnosis of symptomatic severe mitral regurgitation of post-inflammatory aetiology
09 February 2018	Mitral valve reconstruction (annuloplasty ring)
28 March 2018	Mitral valve replacement due to recurrent moderate to severe mitral regurgitation; restriction of the posterior leaflet
March 2018 to April 2018	Intensive care unit stay with open chest treatment, haemorrhagic shock and intermittent haemodialysis
April 2018 to June 2018	Cardiac rehabilitation programme
June 2018 to October 2018	Stabile post-operative phase
08 October 2018	Pulmonary oedema due to mechanical valve thrombosis
19 October 2018	Successful thrombolysis with low-dose, ultra-slow infusion of tissue plasminogen activator
February 2019	Normal function of the prosthesis, INR target 3–3.5

Case presentation

A 52-year-old woman presented to the emergency department with dyspnoea, chest pain, and haemoptysis. She was haemodynamically stable (blood pressure 137/85 mmHg, heart rate 85/min, respiratory rate 22/min) with signs of cardiac congestion. The physical examination revealed mild bilateral ankle oedema with bilateral basal crackles and a systolic click without additional heart sounds. She underwent a mitral valve replacement with a mechanical prosthesis (St. Jude Medical 25 mm) 7 months ago, because of recurrent moderate to severe mitral regurgitation after mitral valve repair in the same year due to symptomatic severe primary mitral regurgitation of (post-)inflammatory aetiology. Her electrocardiogram and chest X-ray were unremarkable. However, plasma N-terminal prohormone of brain natriuretic peptide was significantly elevated (6944 ng/L, $N < 249$ ng/L), and her serum creatinine was 129 μ mol/L ($N < 80$ μ mol/L) consistent with her well-documented chronic renal failure.

Her current pharmacological therapy on admission was Phenprocoumon 1.5 mg OD, Bisoprolol 10 mg OD, Levothyroxine 0.1 mg OD, Pantoprazole 40 mg OD, Montelukast 10 mg OD, and Budesonide/Formoterol Inh 0.4 + 0.012 mg bid. Despite being on oral anticoagulation therapy because of mechanical mitral valve prosthesis, her INR was below her target range (2.3). Hs-troponin (101 ng/L, $N < 14$ ng/L) and C-reactive protein (24 mg/L, $N < 5$ mg/L) were slightly elevated.

The emergency TTE revealed a markedly elevated diastolic trans-mitral pressure gradient of 21 mmHg with impaired movement of one of the prosthesis discs. The last documented transvalvular gradient in our institution was 4 mmHg before discharge after the mitral valve replacement (20 April 2018). Left ventricular systolic function was normal and no mass was visualized in conjunction with the prosthesis. However, the atrial part of the mechanical prosthesis was not demonstrated sufficiently because of shadowing and reverberation artefacts (Figure 1). Fluoroscopy revealed an immobile anterior disc of the mitral prosthesis. Transoesophageal echocardiography confirmed the severe stenosis of the mitral prosthesis due to an immobile anterior disc, but no mass could be detected (Figure 2).

Based on the medical history with acute onset of symptoms, inadequate anticoagulation, and restricted leaflet motion we diagnosed a PVT and initiated a therapy with diuretics and IV unfractionated heparin. We performed a PET/CT scan that excluded inflammation and showed a minor lesion on the atrial and ventricular side of the septal hinge point of the mitral prosthesis without involvement of the prosthesis ring (Figure 3). Five days after IV unfractionated heparin in high therapeutic range the severity of the mitral stenosis remained unchanged. Therefore, we performed a 'low-dose, ultra-slow' fibrinolytic therapy with 25 mg Alteplase; a tissue plasminogen activator (t-PA), without a bolus and with an infusion period of 25 h, as proposed in the focused update of the Americal College of Cardiology (ACC) guidelines for the management of valvular heart disease (2017). This fibrinolytic schema was repeated the day after, thus a cumulative dose of 50 mg t-PA was administered, after a pause of 15 h with unfractionated heparin in therapeutic range. We decided for this treatment because it is associated with a lower bleeding risk. The TTE performed on the next day confirmed successful resolution of the

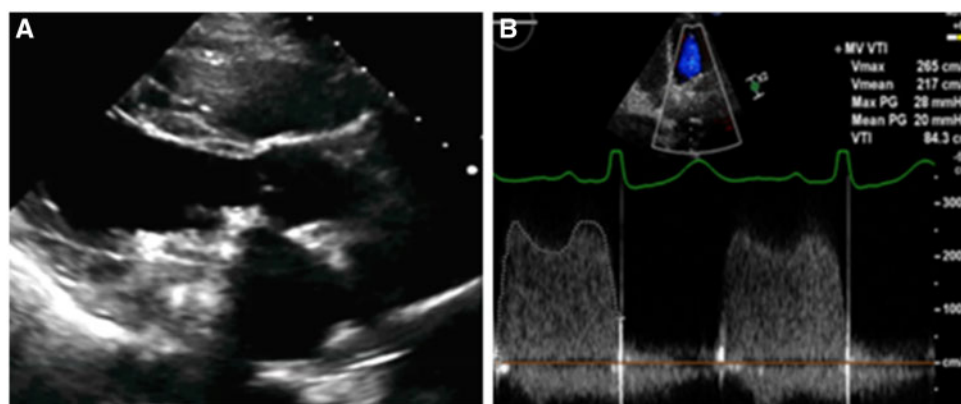


Figure 1 (A) Parasternal long axis (PLAX) in transthoracic echocardiography. The atrial part of the mechanical prosthesis is not sufficiently visualized due to reverberation artefacts. (B) Transmitral diastolic pressure gradient acquired from apical four chamber view (4CV) showing a severe stenosis.

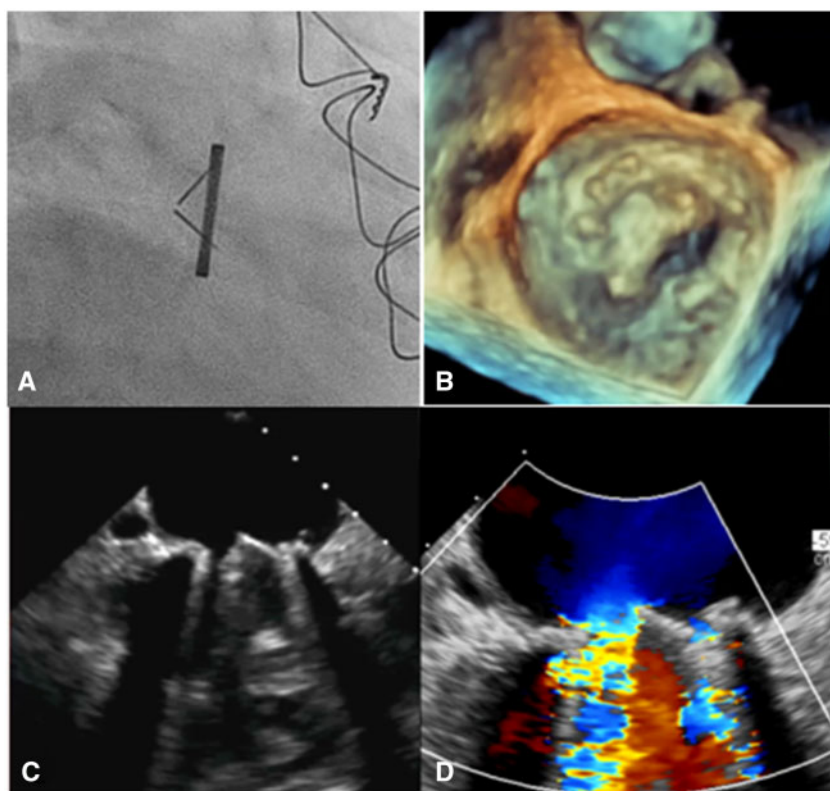


Figure 2 (A) Fluoroscopy showing the immobile anterior disk of the prosthesis. (B) Three-dimensional transoesophageal echocardiography confirming the finding in fluoroscopy. (C) Transoesophageal echocardiography (2CV) showing the immobile anterior disk. (D) Transoesophageal echocardiography (2CV) with colour Doppler showing the acceleration of mitral inflow suggestive of significant stenosis.

thrombus as the motion of the prosthesis discs was normal and the diastolic pressure gradient had returned to baseline values (Figure 4).

On discharge, we intensified the oral anticoagulation with Phenprocoumon 1.5 mg setting a higher INR target range (INR 2.5–3.5), reduced the dose of Bisoprolol to 5 mg OD, and started with

Lisinopril 2.5 mg OD. She remained on Levothyroxine 0.1 mg OD, Pantoprazole 40 mg OD, and Montelukast 10 mg OD. The antiobstructive therapy with Budesonide/Formoterol Inh was stopped.

After discharge, the patient has been regularly seen in our outpatient clinic. She has been doing well and has no cardiac symptoms.

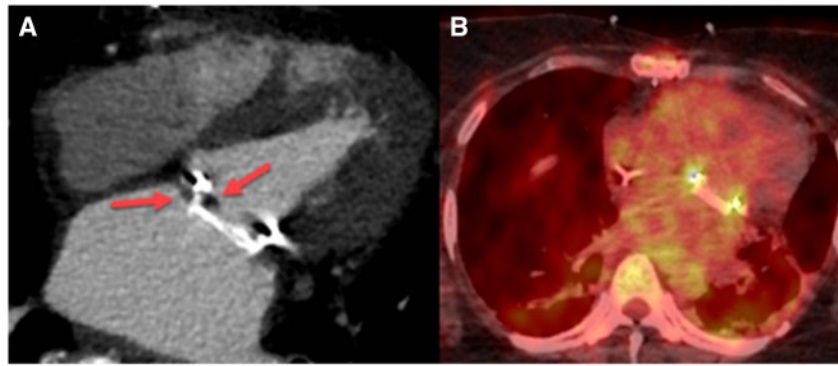


Figure 3 (A) Computed tomography showing two small lesions on the septal hinge point of the prosthesis suggestive of small thrombi. (B) Normal signal intensity of valve prosthesis 7 months after implantation without suspicion of infective endocarditis.

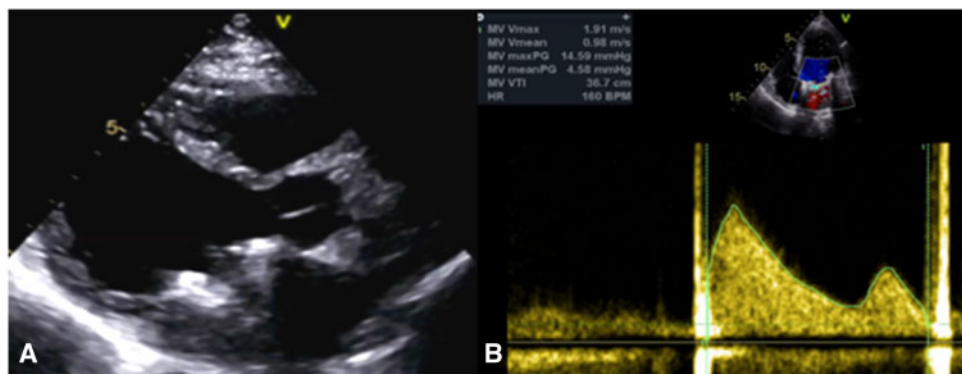


Figure 4 (A) PLAX in transthoracic echocardiography after thrombolysis allowing good visualization of the disks with normal opening. (B) Apical 4CV with normalization of the transmittal diastolic pressure gradient after thrombolysis.

The last echocardiography was performed 4 months after discharge showing a normal function of the mitral valve prosthesis. Due to difficulties in dose adjustment of oral anticoagulation therapy with Phenprocoumon, we perform a regular control of her INR value on a weekly basis and individually adjust the dose in correspondence with her pharmacist in order to remain in the INR target range of 2.5–3.5.

Discussion

In order to determine the adequate therapeutic range of anticoagulation in patients with mechanical valve prosthesis, not only the thrombogenicity of the valve but also the individual thrombotic risk of the patient should be taken into consideration. Patients with atrio-ventricular valve prosthesis, heart failure, atrial fibrillation, or previous thrombosis are known to be at high risk for thrombosis. The reported incidence of symptomatic obstructive mechanical valve thrombosis ranges from 0.3% to 1.3% per year. Although mechanical valve thrombosis is by far more often, thrombosis of bioprosthesis has been reported after surgery and catheter valve implantation.

Subclinical PVT is more common than symptomatic, especially when assessed with cardiac CT.²

The clinical history may imply the underlying aetiology of dysfunction as acute onset of symptoms and history of inadequate anticoagulation are highly suggestive of thrombosis.

If stenosis of a mechanical mitral prosthesis is suspected, but no mass can be detected by TTE and/or TEE or the mobility of the prosthesis leaflets is not impaired, further investigation with cardiac CT is needed in order to differentiate between pannus or thrombus.³ Computed tomography is more sensitive in detecting small lesions as it has higher spatial resolution in comparison to TTE/TEE. Furthermore, the localization of a lesion in combination with its signal intensity measured in Hounsfield Units (HU) may allow the differentiation between pannus and thrombus.^{4,5} Thrombus typically involves the hinge points of the prosthesis and lower HU (<90) are measured, while pannus usually involves the circumference of the prosthesis and higher HU (>140) are expected.⁶

Urgent valve surgery or thrombolysis are both associated with high morbidity and mortality.^{7,8} In case the patient is critically ill, urgent valve surgery should be performed. If the surgical risk exceeds

the bleeding risk or valve surgery is not available, thrombolysis is an alternative therapy. The European guidelines for management of valvular heart disease propose a normal dose thrombolysis (10 mg bolus + 90 mg in 90 min) with t-PA which is associated with high bleeding and stroke risk. The focused update of the American guidelines recommends an alternative thrombolytic treatment algorithm of 'low-dose, ultra-slow' t-PA infusion based on observational studies.⁹ Hence, only 25 mg of t-PA without a bolus and with an infusion period of 25 h is applied and this procedure exhibited the same efficacy with lower bleeding risk. After thrombolysis, unfractionated heparin with a target activated partial thromboplastin time (aPTT) of 1.5–2.0 times the control value is applied for 6 h and in case of recurrent stenosis, the regime could be repeated until a maximal dose of 200 mg. Most patients are expected to require three or fewer infusions and the reported success rate is up to 90% with a non-fatal complication rate of 4% and just one case of in-hospital death.^{10,11}

Conclusions

In the absence of mass on the prosthesis in TEE or if the mobility of the prosthesis leaflets is not impaired, CT may improve the detection and help the differentiation between pannus and thrombus. Low-dose, ultra-slow fibrinolysis should be considered as an alternative to normal dose fibrinolysis or urgent surgery.

Lead author biography



Ioannis Kapos completed his residency programme in cardiology and is board member since 2016. His special interests are in cardiac imaging (echocardiography and cardiac MR) as well as advanced heart failure.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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